isolated pure by preparative layer chromatography on alumina (elution 3 times with hexane) (0.116 g, 50%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (t, J = 6 Hz, 3 H, CH_3), 1.07 (d, J = 6 Hz, 3 H, CH_3), 1.25, 1.40, 1.60 (4 m, 4 H, H-7, 8), 1.82, 1.96 (2 dm, 2 H, H-$5_{ax,eq}$), 2.88 (m, 1 H, H-2), 3.09 (m, 1 H, H-6), 3.42, 3.65 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.55 (ddt, J = 10, 3.5, 2.5, 1.5 Hz, 1 H, H-3), 5.72 (dtd, J = 10, 4, 3.5, 2 Hz, 1 H, H-4), 7.3 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) (Table III); MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 20%), 214 (22%), 177 (100%), 91 (90%); exact mass, 229.1830; calcd for $C_{16}H_{23}N$, m/e 229.1830.

1-Benzyl-*cis*-2-propyl-6-methyl-3-piperideine (22). *n*-Propylmagnesium bromide (4.7 mL, 2.35 mmol) was added dropwise to a cold (-40 °C) solution of amino nitriles **3b** (0.250 g, 1.18 mmol) in THF (10 mL) N_2 atmosphere). The resultant mixture was stirred for 15 min, at -40 °C followed by 45 min at room temperature. After addition of water and normal extractive workup with CH_2Cl_2 a near colorless oil (0.255 g) was obtained. GC analysis of the crude product mixture (SE-30, 155 °C, 1.2 bar) revealed the presence of two isomeric products **21** (T_R = 6.5 min) and **22** (T_R = 6.9 min) in a 17:83 ratio. The desired cis compound **22** was obtained pure after preparative layer chromatography on alumina (elution 3 times with hexane) (colorless oil, 0.170 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 6 Hz, 3 H, CH_3), 1.00 (d, J = 6 Hz, 3 H, CH_3), 1.25, 1.35, 1.5, 1.7, 1.88, 2.05 (6 m, 6 H, H-5, 7, 8), 2.85 (m, 1 H, H-6), 3.06 (m, 1 H, H-2), 3.70, 3.80 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.60 (dq, J = 10, 2, 2, 2 Hz, 1 H, H-3), 5.70 (dqn, J = 10, 4, 2, 2 Hz, 1 H, H-4), 7.3 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) (Table III); MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 5%), 214 (8%), 177 (96%), 91 (100%); exact mass, m/e 229.1816; calcd for $C_{16}H_{23}N$, m/e 229.1830.

1-Benzyl-*trans*-2-propyl-6-methyl-4-piperideine (24). As described for the preparation of **21**, a solution of amino nitrile **15b** (0.250 g, 1.18 mmol) in THF was reacted with LDA (2.0 equiv), and propyl bromide (0.5 mL) (-40 °C, 3 h). After extraction the crude product (0.230 g) was reacted with $NaBH_4$ (30 min, room temperature). A near colorless oil (0.180 g) was obtained containing products **24** (T_R = 5.7 min) and **25** (T_R = 6.0 min) in a ratio of 54/46 (SE -30, 155 °C, 1.2 bar). Product **24** was isolated pure by preparative layer chromatography on alumina (elution 3 times with hexane) (0.067 g, 46%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 6 Hz, 3 H, CH_3), 1.08 (d, J = 6 Hz, 3 H, CH_3), 1.37, 1.53, 1.70, 1.88 (4 m, 6 H, H-3, 7, 8), 2.98 (br qn, J = 6 Hz, 1 H, H-2), 3.03 (m, 1 H, H-6), 3.45, 3.70 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.52 (ddt, J = 10, 4, 2, 2 Hz, 1 H, H-5), 5.75 (dtd, J = 10, 4, 3, 2 Hz, 1 H, H-4), 7.30 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) Table III; MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 10%), 214 (15%), 177 (100%), 91 (88%); exact mass, m/e 229.1828; calcd for $C_{16}H_{23}N$, m/e 229.1830.

1-Benzyl-*cis*-2-propyl-6-methyl-4-piperideine (25). *n*-Propylmagnesium bromide (4.7 mL, 2.35 mmol) was added dropwise to a cooled (0 °C) solution of amino nitrile **15b** (0.250 g, 1.18 mmol) in THF (10 mL) (N_2 atmosphere). The resulting mixture was stirred for 3 h at room temperature. After addition of water and normal extractive workup with CH_2Cl_2 a near colorless oil (0.210 g) was obtained. GC analysis (SE-30, 155 °C, 1.2 bar) revealed the presence of two isomeric products **25** (T_R = 6.0 min) and **24** (T_R = 5.7 min) in a 92:8 ratio. The desired cis compound **25** was obtained pure after preparative layer chromatography on alumina (elution 3 times with hexane) (colorless oil, 0.147 g, 59%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 6 Hz, 3 H, CH_3), 1.05 (d, J = 6 Hz, 3 H, CH_3), 1.25, 1.60 (2 m, 4 H, H-7, 8), 1.85, 2.15 (2 m, 2 H, H-$3_{ax,eq}$), 2.80 (m, 1 H, H-2), 3.30 (m, 1 H, H-6), 3.72 (s, 2 H, $NCH_2C_6H_5$), 5.52 (dq, J = 10, 2, 2, 2 Hz, 1 H, H-5), 5.70 (dtd, J = 10, 4, 4, 2 Hz, 1 H, H-4), 7.30 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) Table III; MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 10%), 214 (22%), 177 (92%), 91 (100%); exact mass, m/e 229.1829; calcd for $C_{16}H_{23}N$, m/e 229.1830.

Acknowledgment. The authors would like to thank M. G. Lemoine (Roussel-Uclaf) for the computer calculations, and Dr. G. Lukacs for helpful discussions concerning the ^{13}C NMR results. We also thank S. K. Kan (Institut d'Electronique Fondamentale, Université de Paris-Sud, Orsay) for the use of his 400-MHz ^{1}H NMR spectrometer.

Registry No. **1a**, 89873-51-8; **1b**, 89873-52-9; **1c**, 89873-53-0; **1d**, 89873-54-1; **1e**, 60900-18-7; **1f**, 89873-55-2; **3a**, 85617-07-8; **3b(A)**, 89873-56-3; **3b(A)** (NCH_3), 89873-57-4; **3b(B)**, 89873-58-5; **3b(B)** (NCH_3), 89873-59-6; **3c(A)**, 89873-60-9; **3c(B)**, 89873-61-0; **3d**, 89873-62-1; **3e**, 73657-71-3; **3f(A)**, 89873-63-2; **3f(B)**, 89873-64-3; **13b(A)**, 89873-65-4; **13b(B)**, 89873-66-5; **15a**, 89873-67-6; *trans*-**15b**, 89873-68-7; **15b** (NCH_3), 89873-69-8; **15c**, 89873-70-1; **15d**, 89873-71-2; **15f**, 89873-72-3; **20**, 89873-73-4; **21**, 89873-74-5; **22**, 89873-75-6; **24**, 89873-76-7; **25**, 89873-77-8; 1-benzyl-6-methylpyridinium bromide, 2654-66-2; 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine, 89873-78-9.

2-Cyano-Δ^3-piperideines. 13.[1] Synthesis and Reactivity of N-Protected Dehydrosecodine Equivalents[2]

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A direct synthesis of 1-(phenylsulfonyl)secodine (**6**) is accomplished by lithiation of 1-(phenylsulfonyl)-3-[2-(5-ethyl-1,2,3,6-tetrahydropyridyl)ethyl]indole (**4**), reaction with methyl pyruvate, and dehydration. The 2-cyano-Δ^3-piperideine derivatives of both the carbinol precursor **9** and of 1-(phenylsulfonyl)dehydrosecodine **12** have been characterized. Various reaction conditions under which 1-(phenylsulfonyl)dehydrosecodine (**14**) could be generated have been examined but no products of either the *Aspidosperma* or *Iboga* structural type have been characterized. Instead, disproportionation of the dihydropyridine intermediate appears to be the dominant reaction. Reductive desulfonylation of the carbinol intermediate provides 16-hydroxy-16,17-dihydrosecodine (isosecodinol) (**19**) but under the same conditions 1-(phenylsulfonyl)secodine (**6**) generates 16,17-dihydrosecodine (**18**).

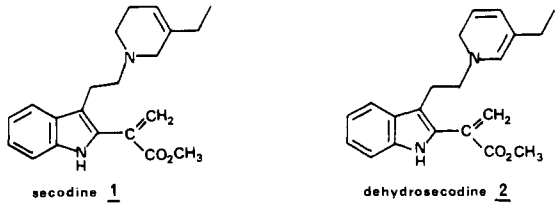
The role of dehydrosecodine (**2**) as an intermediate in the biosynthesis of indole alkaloids (*Corynanthé* → *Strychnos* → *Aspidosperma* and *Iboga*) was postulated by Wenkert in 1962.[4] This hypothesis has been supported

(1) For Part 12 see: Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.*, preceding paper in this issue.

(2) For a preliminary disclosure see: Husson, H.-P. In "Monoterpene Indole Alkaloids"; Saxton, J. E., Ed.; Wiley: New York, 1984.

0022-3263/84/1949-2400$01.50/0

Chart I

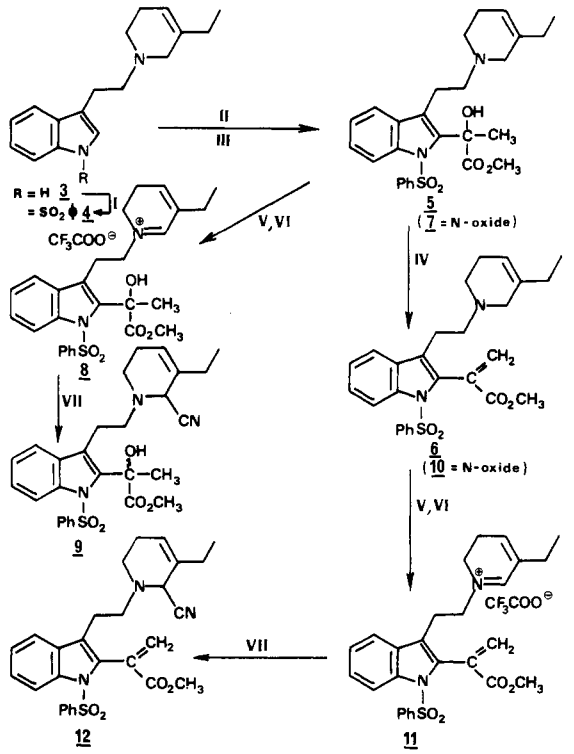


by biosynthetic experiments on the incorporation of labeled secodine by *Catharanthus roseus*[5] (Chart I). The potential role of secodine derivatives as intermediates in the synthesis of indole alkaloids has been well-recognized and a number of derivatives have been reported.[6-11] Only recently, however, was secodine (1) itself prepared.[12] Several of the secodine derivatives can be cyclized efficiently to the *Aspidosperma* alkaloids. The biomimetic synthesis of Kuehne and co-workers[13] based on in situ generation of secodine derivatives or equivalents provides the outstanding example of the efficiency with which the *Aspidosperma* skeleton can be constructed through this route.

The presumably very unstable dehydrosecodine (2) has remained unobserved. Certain derivatives, stabilized by electron-attracting groups, have been prepared but they do not cyclize.[14] The only published report of generation of a reactive dehydrosecodine is that of Kutney, who regenerated the 1-benzyl derivative from a chromium tricarbonyl complex and found a 1.5% yield of *N*-benzylcatharanthine.[15] Thus, a clear documentation of the solution chemistry of dehydrosecodine and, in particular, its partitioning between the *Aspidosperma* and *Iboga* routes for cyclization remains unknown.

We report here our efforts to synthesize 1-(phenylsulfonyl)dehydrosecodine (14). This intermediate, and its subsequent transformations, were of interest for several reasons. Firstly, substitution of the indole N_a–H by the benzenesulfonyl group was expected to retard dimerization which is a competing and limiting process for unsubstituted 2-vinylindoles and indole-2-acrylic acids.[11,16,17]

Scheme I[a]



[a] Reagents: I, OH^-, $Bu_4N^+HSO_4^-$, $C_6H_5SO_2Cl$; II, *t*-BuLi; III, $CH_3COCO_2CH_3$; IV, $POCl_3$-Pyr; V, *m*-CPBA; VI, $(CF_3CO)_2O$; VII, KCN, pH 4.

Secondly, the presence of this group might be expected to favor formation of the *Iboga* skeleton by increasing the reactivity of the acrylic ester group as a dienophile.[18,19] Finally, removal of the benzenesulfonyl group to give natural materials is potentially an easy operation.[20] The 2-cyano-Δ^3-piperideine system was chosen as the immediate precursor of the unstable dihydropyridine unit since it can be generated regioselectively by the modified Polonovski oxidation–cyanide trapping sequence developed in our laboratory.[21] Partial reduction of 3-ethylpyridinium salts leads preferentially to the alternative dihydropyridine.[10,22]

Synthesis of the desired protected secodine proceeded smoothly. The known tetrahydropyridine 3[23] was readily converted to its benzenesulfonyl derivative 4 (Scheme I) under phase-transfer conditions.[24] Lithiation occurred as expected at the 2-position of the indole ring[20] and reaction with methyl pyruvate gave the protected "isosecodinol" (5) in 52% yield. Dehydration with $POCl_3$–pyridine then gave

(3) Department of Chemistry, University of Virginia, Charlottesville, VA. Work done during 1978–1979 while R.J.S. was a visiting research scholar at I.C.S.N. Partial financial support from a Fulbright Research Fellowship is gratefully acknowledged.

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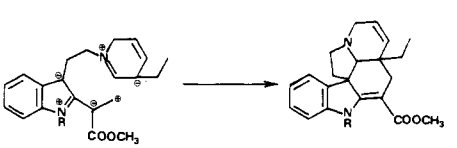
(19) One might also speculate that the benzenesulfonyl group would retard the aspidosperma cyclization if the transition state for that cycloaddition is highly polarized.



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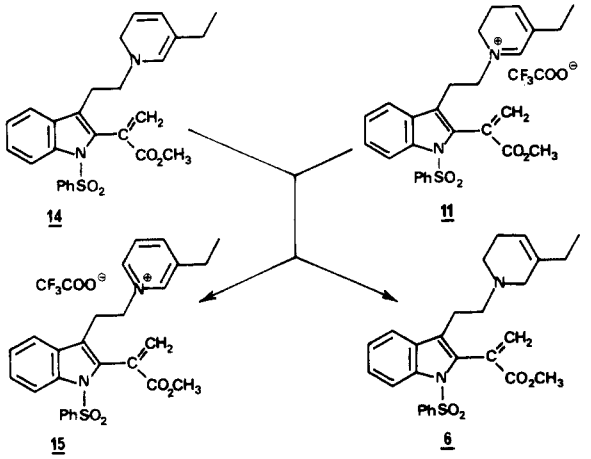
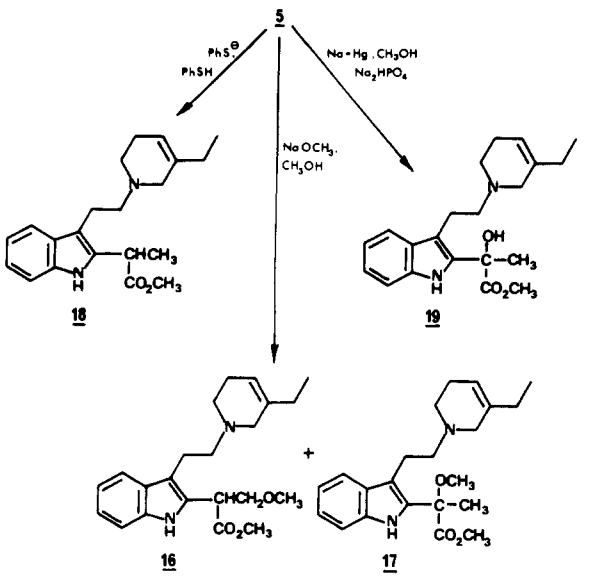
Scheme II



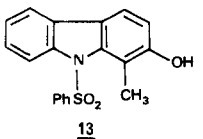
Scheme III



6, an N_a-protected secodine. This represents a very direct and efficient synthesis of this potentially useful intermediate.

Oxidation of 5 with *m*-chloroperoxybenzoic acid, followed by Polonovski–Potier reaction in trifluoroacetic anhydride (CH_2Cl_2, room temperature) and trapping of the resulting conjugated iminium intermediate 8 with cyanide ion[21] ($KCN-H_2O$, pH 4) gave compound 9 in essentially quantitative yield. The dehydrosecodine "equivalent" 12 was also readily prepared by using the cyanide-trapping procedure. Oxidation of 6 with *m*-chloroperoxybenzoic acid occurred selectively at nitrogen. The amine oxide 10, when treated with excess trifluoroacetic anhydride generated the iminium intermediate 11 which could be isolated in good yield as the cyanide adduct 12. With these stable crystalline compounds in hand, possessing an oxidation level equivalent to that of dehydrosecodine, we undertook an investigation of these materials, with the goal of generating the crucial 1-(phenylsulfonyl)dehydrosecodine intermediate 14. Our studies directed toward the synthesis of the *Corynanthé* type alkaloids have shown that it is possible to obtain the conjugated iminium ion of the dihydropyridine structure from such 2-cyano-Δ^3-piperideines.[23]

The reactions of 12 were investigated under a variety of conditions. In refluxing acetonitrile or methanol containing DBU compound 12 decomposed. Reaction also occurred with sodium methoxide in methanol at room temperature but the reaction mixtures were complex, none of the products being clearly identifiable. TLC comparison with samples of the benzenesulfonyl derivative of catharanthine and ψ-catharanthine indicated that no more than traces, if any, of these compounds could have been present in these mixtures. Heating 12 in anisole to 135–145 °C for 3 h gave a material identified by mass spectrometry and NMR as the carbazole 13. An analogous transfor-



mation is known as a thermal degradation pathway for the indole alkaloids,[25] and a mechanism proceeding through dehydrosecodine has been postulated by Scott.

These experiments indicated that 12 was too stable for regeneration of the dehydrosecodine under conditions where it could react cleanly. We then turned to an examination of the reactivity of the iminium ion 11, which is the conjugate acid of the desired 1-(phenylsulfonyl)-dehydrosecodine (14). Deprotonation of 11 should afford 14. Hence, a variety of reaction conditions for this transformation were examined. Addition of the iminium salt to ethanol–triethylamine led to polar material and regeneration (≃25%) of 6 (Scheme II). Triethylamine in anhydrous THF led to similar results. Addition of the iminium ion to methanol or ethanol also led to recovery of 30–40% of 6, even though it was demonstrably absent from the amine oxide used for the preparation of the iminium salt. In some of these runs a highly polar material, which was present in all the runs, was isolated. This material could not be obtained entirely pure but high-resolution NMR showed peaks characteristic of a pyridinium ring. This polar substance is assigned structure 15. It thus became apparent that the dominant reaction process under these conditions was a *disproportionation* of the dihydropyridine intermediate.

This result suggests a fundamental limitation on the use of the iminium ion 11 as a dehydrosecodine precursor. Since the deprotonation which is involved is a C-deprotonation it can be expected to be kinetically slow, and the dihydropyridine will be generated in the presence of unreacted iminium ion. Evidently, the redox reaction between these two species is sufficiently rapid to dominate the subsequent reactions of 14. Since 11 itself is stable in acidic solution, the occurrence of the disproportionation reaction evidently requires the presence of both 11 and its conjugate base, the dehydrosecodine 14.

Attempted direct decomposition of the amine oxide 10 also evidently led to disproportionation. The oxide was refluxed in acetic acid for 2 h. The only products isolated were 6 and the pyridinium salt 15.

With intermediate 5 in hand we also investigated the question of generation of isosecodinol (19) by deprotection of the indole nitrogen (Scheme III). Several methods of desulfonylation of indoles have been described.[20,26] Reaction with potassium *tert*-butoxide in THF led to rapid reaction of 5 but only highly polar material which showed

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mass spectral peaks in the dimeric range could be obtained. With sodium methoxide in methanol, desulfonylation occurred but was accompanied by methoxide addition to the indole-2-acrylate group. Interestingly, both 16- and 17-methoxy-16,17-dihydrosecodine (**16** and **17**) were obtained. Uncatalyzed addition of methanol to secodine has been reported before,[17] but only the 17-methoxy derivative was observed under these conditions. Benzenethiolate removed the benzenesulfonyl group but also *reduced* the acrylate moiety to give 16,17-dihydrosecodine (**18**).[27] Successful deprotection to isosecodinol (**19**) was obtained by reductive desulfonylation by sodium amalgam in buffered anhydrous methanol.

Application of the sodium amalgam deprotection technique to **6** gave the 16,17-dihydrosecodine (**18**) as the major product. It does not appear that any appreciable amount of secodine accumulates under these deprotection conditions. A reaction run to partial completion at 0 °C gave **18** and unreacted **6**. The product contained neither **16**, which might have been formed by methanol addition to secodine, nor secodine dimers.

Experimental Section

1-(Phenylsulfonyl)-3-[2-(5-ethyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]indole (4). A solution of 3-[2-(5-ethyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]indole (**3**) (1.26 g, 5 mmol) in toluene (25 mL) was treated with 165 mg of tetrabutylammonium bisulfate and then stirred vigorously with 5 mL of 50% aqueous KOH. To this mixture was added a solution of benzenesulfonyl chloride (1.5 g) in toluene (25 mL). After stirring vigorously for 1 h an additional 0.5 g of benzenesulfonyl chloride was added. The mixture was stirred for 1 more h. The organic layer was washed several times with water, dried, and evaporated to give **4** as an oil (1.77 g, 90%) which was pure to TLC. For use in the subsequent reaction the material was eluted through a short column of basic alumina and thoroughly dried under vacuum.[23]

Methyl 1-(Phenylsulfonyl)-3-[2-(5-ethyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]-α-hydroxy-α-methylindole-2-acetate (5). A solution of **4** (940 mg, 2.4 mmol) was dissolved in anhydrous THF (20 mL) and the solution was cooled to −10 °C. There was slowly added by syringe 1.30 mL of 2 N *tert*-butyllithium. The solution was stirred for 0.5 h at −10 to −5 °C. It was then transferred by syringe to a solution of methyl pyruvate (2 mL) in THF (20 mL) at −78 °C. The addition was carried out over about 15 min, with the lithiation solution being transferred in small portions to minimize warming to room temperature. After the addition was complete, the solution was kept at −78 °C for 10 min and then quenched with a solution of 1 mL of acetic acid in 5 mL of methanol. The cold mixture was poured into dichloromethane and the solution was washed with aqueous sodium carbonate solution. After drying and evaporating, the oil was separated by chromatography on Merck Alumnium Oxide 90, Activity II–III, using 3:3:1 CH_2Cl_2:hexane:ethyl acetate for elution. The major product, **5** (630 mg, 52%), was obtained as an oil and this material was used in most subsequent experiments. It contains about 5% of the double bond isomer arising from the reductive preparation of **3**.[23] A crystalline sample of **5** was obtained by crystallization from ether: mp 154–155 °C; NMR δ 5.3 (=CH—), 3.8 (OCH_3), 1.7 (CCH_3), 0.65 (CH_2CH_3); MS, m/z 496, 437, 355, 296, 253, 214, 183, 172, 124. Anal. Calcd for $C_{27}H_{32}N_2O_5S$: C, 65.3; H, 6.5; N, 5.6. Found: C, 64.9; H, 6.6; N, 5.6. The separation also usually returned about 10% of unreacted **1** and about 10% of desulfonylated **3** in addition to the major product.

Preparation of the Amine Oxide 7. A solution of **5** (75 mg, 0.015 mmol) in 10 mL of dichloromethane was stirred with 15 mL of water containing 200 mg of sodium bicarbonate. *m*-Chloroperoxybenzoic acid (1.1 equiv of oxidant) was added and the solution was stirred for 30 min. TLC monitoring showed the complete disappearance of amine and appearance of a much more polar material. The organic layer was separated and the aqueous layer was extracted with additional dichloromethane. The combined extracts were dried and evaporated and the residue was purified on a "basic" alumina TLC plate by using 3:2:1 CH_2Cl_2:ethyl acetate:ethanol for development. An unidentified somewhat less polar impurity was removed by this process. The *N*-oxide layer was leached from the plate and dried to give a hard glass. A solid form of the amine oxide was obtained by trituration with ethyl acetate: NMR 5.05 (=CH—), 3.75 (OCH_3), 2.0 (CCH_3), 0.9 (CH_2CH_3); MS, m/z 437, 385, 326, 284, 185, 184, 124. Anal. Calcd for $C_{27}H_{32}N_2O_6S\cdot 0.5H_2O$: C, 62.1; H, 6.4; N, 5.4. Found: C, 61.8; H, 6.2; N, 5.0.

Methyl 1-(Phenylsulfonyl)-3-[2-(6-cyano-5-ethyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]-α-hydroxy-α-methylindole-2-acetate (9). The glassy form of the amine oxide **7** was normally used. A solution of the oxide (50 mg) in CH_2Cl_2 (20 mL) was treated with an excess (250 mg) of trifluoroacetic anhydride at ambient temperature. The reaction was followed by TLC until all the oxide had disappeared (3 h) and, if necessary, additional trifluoroacetic anhydride (100 mg) was added. A solution of potassium cyanide (150 mg) in 2–3 mL of water was added and the pH was adjusted to 4 with sodium acetate. The solution was stirred for 15 min, made alkaline with sodium carbonate solution, and extracted with methylene chloride. TLC showed formation of a single major product which was purified to give **9** (52 mg) as a white solid: NMR δ 5.6 (=CH—), 3.65, 3.70 (OCH_3), 2.0 (CCH_3), 1.05 (CH_2CH_3), doubling of the OCH_3 and CH_2CH_3 peaks indicates a diastereomeric mixture; MS, m/z 521, 496, 462, 437, 407, 385, 381, 365, 326, 284, 229, 216, 214, 201, 185, 184, 176, 149. Anal. Calcd for $C_{28}H_{31}N_3O_5S$: C, 64.5; H, 6.0; N, 8.1. Found: C, 64.3; H, 6.1; N, 7.9.

Methyl 1-(Phenylsulfonyl)-3-[2-(5-ethyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]indole-2-acrylate (6). A solution of **5** (100 mg, 0.20 mmol) was dissolved in 8 mL of anhydrous pyridine and treated with a solution of 1.3 g of phosphorus oxychloride dissolved in 5 mL of pyridine. The solution was heated to 110–120 °C for 2 h. The solution was then cooled and carefully poured onto ice. The mixture was brought to pH 9 with aqueous sodium carbonate and extracted with CH_2Cl_2. The crude product was purified by elution through alumina followed by preparative-layer chromatography on "basic" alimina using 3:1:1 CH_2Cl_2:hexane:ethyl acetate for development. The pure product (37–55 mg, 38–58%) was obtained as a gum: NMR δ 6.7, 5.7 (=CH_2), 5.5 (=CH—), 3.8 (OCH_3), 1.0 (CH_2CH_3); MS, m/z 478, 447, 337, 228, 168, 167, 154, 124, 77.

Preparation of Amine Oxide 10. A solution of **6** (48 mg, 0.10 mmol) in CH_2Cl_2 (20 mL) was mixed with 2 mL of water containing 80 mg of $NaHCO_3$ and treated with 23 mg of *m*-chloroperoxybenzoic acid. After 30 min TLC indicated complete disappearance of the amine. The workup was as for **7**. The product mixture gave a major product (40 mg) which showed that the acrylate group and piperidine double bond had remained unaffected: NMR δ 6.7, 5.6 (C=CH_2), 5.5 (=CH—). This oxide is unstable and is converted to a much less polar material on standing. It was refrigerated and used within 24 h.

Methyl 1-(Phenylsulfonyl)-3-[2-(6-cyano-5-ethyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]indole-2-acrylate (12). A sample of **6** (100 mg) was converted to **10** following the above procedure. The oxide was dissolved in CH_2Cl_2 and treated with trifluoroacetic anhydride (900 mg). When disappearance of the amine oxide was complete, 120 mg of potassium cyanide was added. This mixture was stirred for 15 min and then the pH was adjusted to 4 with sodium acetate. The product was obtained by the usual extraction process, purified by thick-layer chromatography, and crystallized from hexane–ethyl acetate: mp 130 °C (78 mg, 74%). Anal. Calcd for $C_{28}H_{31}N_3O_4S$: C, 66.8; H, 5.8; N, 8.3. Found: C, 66.4; H, 5.9; N, 8.0.

Reactions of 5. A. With Sodium Methoxide in Methanol. A solution of sodium methoxide in anhydrous methanol (20 mL) was prepared by dissolving sodium metal (350 mg, 15 mmol). To this was added 60 mg of compound **5** and the solution was refluxed 0.5 h. The reaction mixture was neutralized to pH 7 by addition of acetic acid in methanol and most of the methanol was removed in vacuo. The residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The product consisted of two major components which were resolved on basic alumina by using 2:1:1 CH_2Cl_2:hexane:ethyl acetate. The less polar material (10

(27) Previously reported in ref 6 and 25.

mg, 20%) was identified as 17-methoxy-16-17-dihydrosecodine: NMR δ 8.8 (NH), 5.6 (=CH—), 3.9 (CO_2CH_3), 3.5 (CH_2OCH_3), 4.3 ($—CH_2OCH_3$, m), 1.15 (OCH_2CH_3, t). The more polar product (16 mg, 33%) was 16-methoxy-16,17-dihydrosecodine: NMR δ 8.9 (NH), 5.65 (=CH—), 3.9 (CO_2CH_3), 3.45 ($COCH_3$), 2.1 (>CCH_3), 1.1 (CH_2CH_3).

B. With Lithium Thiophenoxide. A solution of lithium thiophenoxide–thiophenol was prepared by addition of 2 N *tert*-butyllithium (1 mmol) to thiophenol (300 mg, 2.75 mmol) in anhydrous THF (25 mL). To this solution there was added 75 mg of compound **5** and the solution was refluxed for 5 h. The reaction mixture was then treated with a little methanol, diluted with methylene chloride, and washed throughly with sodium carbonate solution. TLC identified a single major product which was purified by preparative TLC to give 16,17-dihydrosecodine (30 mg, 60%): NMR δ 8.5 (NH), 5.6 (=CH—), 3.8 (OCH_3), 1.6 ($HCCH_3$), 1.15 (CH_2CH_3); MS, *m/z* 340, 309, 281, 230, 229, 216, 184, 170, 156, 125, 124.

C. With Sodium Amalgam in Methanol. A solution of **5** (~25 mg) was dissolved in 30 mL of anhydrous methanol. At three 1.5-h intervals there was added dry Na_2HPO_4 (250 mg each addition) and 5% sodium amalgam (150 mg each addition). The reaction mixture was then poured into 1% NaOH solution and extracted with methylene chloride. The solution was dried and evaporated to give the isosecodinol (**19**): NMR δ 8.50 (NH), 5.5 (=CH—), 3.81 (OCH_3), 1.90 (CCH_3), 1.03 (CH_2CH_3).

Thermal Decomposition of 12. A solution of **12** (10 mg) in distilled anisole (2 mL) was sealed in a small ampule and heated to 140 ± 5 °C for 3 h. The solution was cooled and the anisole was removed in a kugelrohr apparatus. The residue was purified on silica using ethyl acetate:hexane for elution to give **13**: NMR δ (recorded at 360 MHz) 8.11 (d), 7.45 (d), 7.38 (d), 7.2–7.35 (m), 7.0–7.10 (m), 6.90 (d), 2.70 (s).

Reduction of 6 with Sodium Amalgam. Reduction of **6** under the conditions described for **5** gave **18**. A reduction run at 0 °C using 10 mg of **6** and a single addition of Na_2HPO_4 and Na–Hg was terminated after 1 h. TLC indicated unreacted **6** and **18** as the principal components. This mixture was kept in a dilute methanol solution for 48 h at 0 °C. The mass spectrum of this material showed neither a methanol adduct nor a dimer derived from secodine.

Registry No. **3**, 82980-06-1; **4**, 82980-08-3; **5**, 89850-26-0; **6**, 89850-28-2; **7**, 89850-27-1; **9**, 89873-84-7; **10**, 89850-29-3; **12**, 89850-30-6; **13**, 89850-33-9; **17**, 89850-31-7; **18**, 27825-43-0; **19**, 89850-32-8; methyl pyruvate, 600-22-6.

Synthesis and Characterization of Anhydro-1,1-dialkyl-5-hydroxy-3-phenoxy-1,2,4-triazolium Hydroxides

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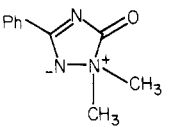
1,1-Dialkylhydrazines and phenyl *N*-(chlorocarbonyl)-1-chlorocarbonimidate react to give excellent yields of anhydro-1,1-dialkyl-5-hydroxy-3-phenoxy-1,2,4-triazolium hydroxides. The reaction is regiospecific, and the same products are obtained from phenyl N^3,N^3-dialkylcarbazimidate and phosgene. Thiophosgene and isocyanide dichlorides give exocyclic sulfur and nitrogen containing zwitterions, respectively. Alkylation of the triazolium hydroxides occurs exclusively on N2, and an *O*-Ph to *N*-Ph migration was observed at ca. 205 °C. Via dynamic NMR experiments, the diasteriotopic methylene hydrogens of the benzyl groups attached to the quaternary nitrogen atom gave thermodynamic exchange data of E_a = 21.7 ± 0.7 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 21.0 ± 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ = 6 ± 1 eu, and $\Delta G^{\ddagger}$ = 19.3 ± 0.5 kcal mol^{-1}.

As part of a conceptual approach to heterocyclic synthesis,[2] we have been investigating the reactions of appropriately substituted bielectrophiles with binucleophiles leading to heterocyclic zwitterions.[3-5] In this publication we describe our results utilizing 1,1-dialkylhydrazines as the 1,2-binucleophilic component.

Cyclic aminimides containing a pyrazole nucleus have been prepared[6] by the reaction of α,β-unsaturated esters, acid chlorides, or acid anhydrides with 1,1-dialkylhydrazines, by alkylation of the parent pyrazolinone, or by condensation of the pyrazolinone with an aldehyde or ketone. In contrast, relatively few ylides have been incorporated into the 1,2,4-triazole system, but successful syntheses have resulted from the reaction of 1,1-dimethylhydrazine with *N*-(α-chlorobenzylidene)carbamoyl chloride[7] giving **1**, from the dimerization of dialkylamino



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isocyanates,[8] and from the cycloaddition of amino isocyanates with heterocumulenes.[9] The above 1,1-dimethylhydrazine cyclocondensation could give isomeric products, and the structure **1** was assigned[7] solely on the basis of ν_{CO} 1765 cm^{-1}.

Phenyl cyanate readily adds phosgene in the cold to give phenyl *N*-(chlorocarbonyl)-1-chlorocarbonimidate (**2**) containing two highly electron deficient carbon atoms. The chlorine of the formyl group is more reactive, and both chlorines may be replaced[10] successively with appropriate

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